REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendment are respectfully requested.

Claim 31 has been cancelled without prejudice. That the claim has been deleted should not be taken as an indication that Applicants agree with any position taken by the Examiner. Rather, the claim has been deleted merely to advance prosecution and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

Cancellation of claim 31 renders moot the rejections thereof under 35 USC 101 and 35 USC 112, as well as the objection thereto.

Prior to addressing the Examiner's art-based rejections, Applicants offer the following comments regarding the presently claimed invention.

In the covalent display approach of the present invention, double-stranded DNA encoding a *cis*-acting protein, for example, P2-A, fused to a plurality of polypeptide sequences is incubated in an *in vitro* transcription and translation reaction. The *cis* activity of, for example, P2-A ensures that the expressed polypeptides bind faithfully and covalently to the same molecule of DNA that served as the template for their expression.

The protein-DNA complexes are used for the affinity selection of target-binding polypeptides. The covalent association and co-selection of the DNA that encoded the target-binding polypeptides enables the recovery and identification of the relevant sequences (a specific embodiment of the invention is shown in Figure 1 merely for purposes of exemplification – this Figure was previously provided with the Amendment filed July 22, 2004).

Turning now to the Examiner's specific concerns, claims 21, 22, 24, 26, 27, 28, 31, 34-36 and 39 stand rejected under 35 USC 102(e) as allegedly being anticipated by Maruyama et al. The rejection is traversed for the reasons that follow.

The method of Maruyama involves the use of lambdoid phages as alternatives to the use of filamentous phages for the phage display of polypeptides. The Maruyama method is conceptually identical to phage display as practiced using the filamentous phage M13. It involves the construction of a plurality of modified phage genomes in which the gene for one of the phage coat or tail proteins is fused in frame with a population of genes for display. Upon insertion of the pool of genomes into an appropriate *E.coli* host (transformation), the phage genome replicates and results in the production of progeny phage in which the phage head structure contains the modified genome and the tail structure displays the polypeptide encoded by the fused gene within the modified genome (see attached Figure 7 which supplements the Figures submitted with the Amendment filed July 22, 2004).

In rejecting the claims as anticipated, the Examiner refers to the following sections of Murayama:

- Column 16, lines 10-45, where, according to the Examiner "the formula of a fusion of the polypeptide to its DNA encoding sequence" is disclosed. This is represented by the formula NH_2-O-U-V-COOH, where O represents an amino acid residue sequence defining a lambdoid matrix anchor polypeptide (a portion of a phage coat protein or tail protein), U represents a linker polypeptide and V represents an amino acid residue.
- Column 16, line 20, where it is stated that "a preferred polypeptide comprises a preselected polypeptide operatively linked at is amino-terminus to the lambdoid matrix anchor polypeptide".
- Column 16, line 40, where it is stated that "'operatively linked' means that the polypeptide fragments ... have been covalently joined ...".
- Column 2, lines 29-34, where it is stated that the "multimeric polypeptides and the genes which encode the polypeptides are thus physically linked during the assembly stage of the phage replication cycle".
- Column 8, lines 62-63, where it is disclosed that the lamdoid phage particles are about half protein and half DNA.

Nothing in Maruyama, including the above-referenced portions, teaches the existence of a direct covalent interaction between the displayed polypeptide (e.g., the product of the formula F1 as stated in column 16, lines 10-20) and the DNA that encoded it. Indeed, the disclosures of Maruyama suggest that the only components of the method that are covalently linked are the displayed polypeptide and the lambdoid matrix anchor polypeptide itself (i.e., NH_2-O-U-V-COOH) which are fused via a linker peptide through standard peptide bonds. Nowhere does it state that there is any "fusion" between the product of formula F1 and "its DNA encoding sequence".

Furthermore, the Murayama method is entirely reliant on the assembly of phage particles during the phage replication cycle whereas, for the practice of covalent display, the use of phage particles, mammalian viruses, eukaryotic cells, bacteria or any other biological entities, are not required.

Finally, the DNA:protein complexes that are formed in covalent display are not nearly in a ratio of 50:50, they are in fact closer to a ratio of 10:1. This is because, in addition to the encoding DNA, there is just one protein associated with it, that is, for example, P2-A.

The Murayama technique differs significantly from the covalent display technique of the present invention. Notably, the Murayama method requires the transformation of *E.coli* with the DNA that comprises the modified genome. This then facilitates the production of the lambda phages that display the polypeptides of interest. The physical linkage between the expressed polypeptide and its encoding DNA is, therefore, not through a direct covalent bond between the expressed polypeptide and its encoding DNA, as it is with covalent display, rather it is through

the *in vivo* assembly of a viable phage particle that has the encoding DNA packaged within the head of the particle and the displayed polypeptide attached to the tail protein.

The *cis*-activity of, for example, P2-A obviates the need to perform the transformation step that is common to both M13 and lambdoid phage display. The *cis*-activity of, for example, P2-A enables the linkage between the gene and gene product to be formed without confining individual genes within a bacterial (or any other) cell prior to their transcription and translation. The DNA constructs produced by the Murayama method cannot form a physical linkage between a gene and its expressed polypeptide unless the *in vivo* phage assembly process occurs. Such phage assembly is not required in the covalent display method.

No *cis*-acting DNA binding proteins (as defined for covalent display as being proteins capable of binding covalently to the same DNA molecule that served as the template for their synthesis) are disclosed or contemplated by Murayama.

The mechanisms by which a library of peptides that are linked to their encoding nucleic acids are achieved are thus very different between the Murayama and covalent display methods and, therefore, the covalent display method cannot be considered to be taught or suggested by Maruyama.

In view of the above, reconsideration is requested.

Claims 21, 22, 24-29, 31, 34-36, 39 and 40 stand rejected under 35 USC 103 as allegedly being obvious over Maruyama in view of Lui et al. The rejection is traversed for the reasons that follow.

The distinctions between the present invention and the primary reference are detailed above. As will be clear from the comments that follow, Lui adds noting to Maruyama that would have rendered the present invention obvious.

Lui relates to the construction of individual plasmids containing P2-A wild type, P2-A (Y450D), P2-A (Y454F) or P2-A (Y450D and Y454F). Each P2-A variant was cloned in-frame with a His tag. Proteins were expressed in *E.coli* to produce inclusion bodies. The inclusion bodies were isolated and the P2-A variants purified using the His tags to which they were fused. Biochemical studies were then conducted on purified proteins to understand the catalytic mechanism of P2-A (see attached Figure 2, originally submitted July 22, 2004).

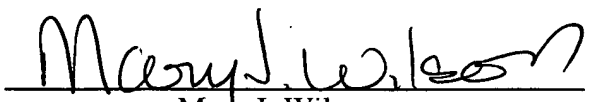
In Lui, there is no disclosure of the recovery of covalent protein:DNA complexes following expression in *E.coli*. Only the expressed and purified protein is recovered for biochemical analyses (cleavage of single stranded oligouncleotides containing the ori sequence). There is no disclosure of the formation of a library consisting of P2-A fused to a plurality of peptides. There is no suggestion in Lui that the cis property of P2A could be exploited for a library screening method.

Given the unrelatedness of Maruyama and Lui, there is nothing in their teachings that would have suggested their combination. Further, even if the references had been combined, that combination would not have rendered the claimed invention obvious. Accordingly, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested. **However, should the Examiner find any matters to be outstanding, she is urged to contact the undersigned by phone so that same can be resolved**.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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